IV. "On the Influence exercised by the Central Nervous System on the Cardiac Rhythm, with an Inquiry into the Action of Chloroform on that Rhythm."* By JOHN A. MACWILLIAM, M.D., Professor of the Institutes of Medicine in the University of Aberdeen. Communicated by Professor M. FOSTER, Sec. R.S. Received March 23, 1893.

The following is a brief account† of the main results obtained in the course of a prolonged investigation of the above subject.

The animals employed were chiefly cats and rabbits, anæsthetised or narcotised with chloroform or chloral hydrate. In the great majority of the experiments, cats were used anæsthetised with chloroform; and it is the results obtained in those circumstances that I am to be understood as specially dealing with in this paper.

The chief object of the present investigation was to examine more fully the mechanism through which changes in the pulse rate are effected and the nature of those changes, when such are dependent on an influence exercised by the central nervous system upon the cardiac rhythm, *e.g.*, the changes in the pulse rate induced by afferent impulses, &c.

In proceeding to examine the influence of the nervous system on the cardiac rhythm, it is necessary in the first place to determine the conditions depending on the presence of the anæsthetic, as far as they bear on the cardiac rhythm, the influence of chloroform upon the heart itself and upon the centres of the cardiac regulating nerves.

I. ON THE RELATION OF CHLOROFORM TO THE CARDIAC RHYTHM.

With a view to the elucidation of this question, I have carried out the following series of experiments, to test the action of chloroform under different conditions and so determine the manner in which it may affect the rhythmic mechanism of the heart:—

1. Experiments in which the entire cardiac regulating mechanism was intact.

2. Experiments after section of the cardiac augmentor nerves, the vagi being left uninjured.

3. Experiments in which the vagi were divided, the cardiac augmentor nerves remaining intact.

4. Experiments in which the whole of the cardiac nerves were divided, all direct connexion between the heart and the central nervous system being thus severed.

* The expenses of this research were for the most part defrayed by a grant from the Royal Society.

† Full details and references are stated in a longer paper, soon to be published.

The main results of these experiments I shall now state briefly:—

1. *Experiments in which the Entire Cardiac Regulating Mechanism was Intact.*

When chloroform is administered by inhalation in the usual way, two well-marked stages are usually evident in its action on the cardiac rhythm:—

A. A stage of acceleration far beyond the ordinary pulse rate of the animal. From the normal rate of 120—130 (cat), the pulse may rise as high as 240—250. The acceleration occurs during the general excitement induced by the anæsthetic.

After a time, as the administration of chloroform progresses, the acceleration diminishes and gives place to the second stage.

B. A stage of moderate or slow pulse rates. In this stage the cardiac rhythm falls towards the normal rate; it may come to be closely similar to the normal rate (120—130 per minute), or it may stand at a higher or a lower level, though within such limits as to render the pulse frequency a comparatively moderate one (90—150 per minute). This stage usually continues during deep anæsthesia, and even when the narcosis becomes very profound and dangerous.

These stages, as seen in the cat, closely resemble, in their general character, the similar phases usually recognisable during the administration of chloroform in man.

It should be mentioned that in some cases the reduction of pulse rate which follows the primary acceleration is comparatively slight, the frequency of the beat remaining high above the normal standard even during profound anæsthesia. The conditions determining such a difference from the usual course of events cannot be discussed here; they are considered in my detailed paper on the subject. In some other other animals (*e.g.*, the hare) the heart commonly beats with great rapidity (260, &c.) even during deep anæsthesia, and in this respect such animals differ notably from the cat and from man.

During a certain period of chloroform anæsthesia the cardiac rhythm may readily be altered to a very important degree—either in the direction of slowing or acceleration—by excitation of afferent nerves or by changes in the blood pressure, &c. The period alluded to comprises the latter part of the first stage or stage of acceleration and the earlier part of the second stage or stage of moderate or slow pulse rate. I do not wish to imply that at no other phase of chloroform administration *can* changes in the heart's rhythm be brought about by similar causes, but only that the period referred to is the one most favourable to their ready manifestation, and the one in which their action is most constant. In the latter part of the second stage the cardiac rhythm passes beyond the influence of afferent impulses.

It need hardly be remarked that if strong chloroform vapour be too suddenly administered, well-marked reflex slowing of the heart may occur, as is well known; and such slowing may precede what I have described as the first stage or stage of acceleration.

Evidence as to the mode in which chloroform brings about the alterations in the cardiac rhythm which have been mentioned is afforded by the results of the subsequent series of experiments.

2. *Experiments after Section of the Cardiac Augmentor Nerves, the Vagi being left Uninjured.*

Those nerves were divided by an operation in which resection of the two uppermost ribs was performed, artificial respiration being maintained; the inferior cervical and the 1st thoracic (stellate) ganglia, together with the annulus of Vieussens, were completely removed on both sides, their connexions with the spinal nerves and the vagi being followed up for a considerable distance and divided. The sympathetic chain was cut through about 2 cm. above the inferior cervical ganglion, and about the same distance below the ganglion stellatum. The vagi themselves were left intact.

No blood vessels were tied, and there was nothing beyond a very inconsiderable loss of blood in the whole proceeding.

When the influence of the cardiac augmentor nerves has been excluded in this way there is no essential change evident in the action of chloroform upon the cardiac rhythm; the stage of acceleration (A) and that of moderate or slow rate (B) are still plainly apparent during the lighter and the more profound phases of anæsthesia. It is clear, then, the augmentor nerves are not the essential channels through which chloroform produced its important effects upon the pulse rate.

3. *Experiments in which the Vagi were Divided, the Cardiac Augmentor Nerves remaining Intact.*

The results obtained in this set of experiments were so essentially similar to those of the following group that the two may be taken together. The presence of the intact augmentor nerves does not seem to be of any essential importance as far as the effect of chloroform on the cardiac rhythm is concerned.

4. *Experiments in which all the Cardiac Nerves were Divided, all Direct Connexion between the Heart and the Central Nervous System being thus Severed.*

In this condition the heart beats very rapidly, being liberated from the controlling influence of the cardio-inhibitory centre in the medulla.

The rate of action rises far above the normal, provided the blood pressure remain good, and the temperature and general condition of the animal continue satisfactory; the pulse rate rises from a normal rhythm of 120—130 to one varying from 216 to as high a figure of 240—250, according to the depth of the anæsthesia and other circumstances.

When the heart is beating in this very rapid fashion the further administration of chloroform deepening the anæsthesia, induces, as a rule, a very distinct reduction in the pulse rate, while at the same time the blood pressure falls markedly. The reduction in the pulse rate is not at all comparable in extent to that which usually follows a similar dose of chloroform while the vagi are intact: the diminution in rapidity in the present case (when the vagi or all the cardiac nerves are cut) is comparatively a slight one, *e.g.*, a reduction from the rate of 240 to one of 200, &c.

But, though the slowing of the rhythm is a much less extensive one than occurs while the vagi are intact, it is at the same time a very appreciable and constant one; and, moreover, it is important, depending as it evidently does on some cause affecting the heart itself, and not exerted through the influence of the regulating (extra-cardiac) nerves.

Now, as to the mode in which this slowing effect is produced in the action of the cardiac mechanism, the possible influence of the markedly-lowered blood pressure has to be taken into account. We know that in certain circumstances a great lowering of the blood pressure may lead to a very pronounced slowing of the pulse rate, and the question arises as to whether such a cause is sufficient to explain the reduction in rate caused by chloroform in the conditions now under consideration. I conclude that it is not, for these reasons:—

1. The diminution in the rate of heart beat may begin *early* when the fall of pressure is only slightly developed, and

2. A similar, or indeed a much greater fall of blood pressure lasting for similar periods, when induced by mechanical causes (*e.g.*, compression of portal vein, &c.), entirely fails to cause any diminution of rate like that which occurs when the pressure is lowered by chloroform. Experiments in which reduction of blood pressure of equal amount and duration were alternately induced by (*a*) chloroform and (*b*) mechanical causes have clearly shown this.

There is good reason to believe that chloroform has a special influence on the rhythmic mechanism of the heart, an influence not dependent on the concomitant lowering of the blood pressure caused by the drug.

Again, as to the nature of the influence exerted by chloroform in this way, it can be shown that the slowing is not dependent on a

stimulation of the local inhibitory mechanism of the heart. For the administration of atropin in doses sufficient to paralyse that mechanism does not obviate the slowing effect of the anæsthetic. (The paralysed condition of the inhibitory mechanism was verified by strong electrical stimulation of the inhibitory area, described in former papers in the 'Proceedings of the Royal Society,' vol. 44, and the 'Journal of Physiology,' vol. 9, 1888.)

From these results it appears that chloroform acts on the heart, and distinctly slows its rate of beat through a depressing or retarding influence exerted on the intrinsic rhythmic mechanism of the organ.

Further, it is evident that the reduction in the pulse rate that occurs in the second stage (B) of chloroform anæsthesia is of a two-fold origin: it partly results from the action of chloroform on the heart itself, but it very largely depends on the integrity of the vagi. The vagus centre in the medulla, though rendered incapable of reflex excitation, is not paralysed even during deep anæsthesia; it continues, as a rule, to exert a very important controlling influence upon the cardiac rhythm, and it is indeed to the exercise of this controlling influence that the reduction of the pulse rate from the excessively high rapidity often present during the stage of acceleration is mainly due. Even during profound anæsthesia, section of the vagi leads, as a rule, to a striking acceleration of the pulse rate, though the rapidity does not become as great as during a lighter anæsthesia. When the anæsthesia is allowed to become less deep the rate of heart beat increases decidedly.

As regards the notable acceleration of the heart which occurs in the first stage (A) of chloroform administration (stage of excitement), this is not to be accounted for by an assumed excitation of the cardiac augmentor nerves, for marked acceleration occurs under the influence of the anæsthetic even when the augmentor nerves have been excluded by section.

On the other hand, the action of chloroform at different stages of its administration on the heart itself after section of all the cardiac nerves shows no ground for assuming that the acceleration might be due to direct influence on the intrinsic rhythmic mechanism.

Moreover, the general indications of excitement in the central nervous system (respiratory centre, &c.) point to the probable occurrence of central changes in the centres of the regulating nerves. And as an assumed activity of the augmentor nerves has been set aside as inadequate to meet the facts, there remain only the vagi. A reduction in the controlling influence of the vagus centre would cause such an acceleration as that which usually occurs, and it is, I believe, to such a change that the quickened pulse rate is mainly, if not entirely, due.

This change—the diminution in activity of the vagus centre—is

not due simply to a fall of blood pressure; it occurs while the blood pressure is still high, and shows no constant relation to alterations in the pressure, sometimes occurring when the blood pressure is rising, and sometimes when it is falling, and at other times when there is no important alteration of level.

The cause of the alteration of phases of slowing and acceleration is to be sought in an alternately increased and diminished activity of the vagus centre. Further evidence regarding the occurrence of such variations in the conditions of the centre will be adduced later in this paper.

In those cases alluded to—when the heart continues to beat at a rapid rate even during profound anæsthesia—the cause appears to lie mainly in a continued suspension of the activity of the vagus centre, a great diminution or a removal of its controlling influence on the heart. In this condition chloroform may still slow the heart, though only to a relatively slight extent, by its direct influence on its intrinsic rhythmic mechanism of the organ.

II. On the Relation of the Heart's Rhythm to Changes in Blood Pressure.

It is well known, since the work of Ludwig and Thiry upon the subject, that changes in blood pressure may affect the rate of the heart's beat otherwise than through the mediation of the cardiac regulating nerves.

Many investigators have dealt with this relation, with wide variations in the results arrived at; and such variation is not surprising when one considers the different conditions that may be present in such experiments, differences as to the animals used, the drugs (curare, chloral, morphia, &c.) administered, the various levels from which the change of blood pressure may start, the duration of such pre-existing level, the character and duration of the change itself, the conditions as regards intra-cardiac tension (in one or more parts of the organ) attendant on changes in the arterial pressure, &c.

In view of such circumstances, I have found it necessary to perform a considerable number of experiments to demonstrate how far the cardiac rhythm was affected by blood pressure changes in such conditions of experiment as those commonly present in the present investigation (simple chloroform anæsthesia, &c.), especially as regards the competency of more or less sudden blood pressure changes of short duration to account for important changes in the rate of the heart's beat.

Such experiments I have performed in the following conditions:—

A. *When the heart was released from all direct influence which may be exercised through the cardiac regulating nerves.*—By section of all

these nerves, or by destruction or death of the medulla and cervical spinal cord (cat and rabbit).

The general results obtained were these:—*a*. In this condition it was found that the existence of an extremely low pressure continuing for some time (minutes) leads to a very pronounced slowing of the pulse rate, and a subsequent elevation of the pressure may cause a more or less extensive acceleration of the beat.

b. An exceedingly high blood pressure may cause marked slowing of the heart through its influence on the intra-cardiac mechanism.

c. When the blood pressure is at a fair height, the occurrence of a great fall of pressure lasting for short periods (*e.g.*, 30 seconds) causes no change in the cardiac rhythm.

Nor does a rise of pressure from this low level—established as it has been for only a brief space of time—to the preceding level, or even a good deal higher, involve any appreciable change in the pulse rate.

A similar negative result is present when, instead of undergoing a fall from the original level, the pressure is made to rise; there is no change in the pulse rate unless the rise attains to such proportions as to induce the slowing mentioned in (*b*).

There can be no doubt that extensive variations in the blood pressure (*e.g.*, between 30—40 mm. and 150—160 mm.) if of brief duration do not as a rule involve any important or constant change in the rate of the heart's beat.

B. *When all the Cardiac Nerves were Intact.*—The results here obtained were in complete accordance with those usually described—a raised blood pressure causing well-marked slowing of the heart, and a fall of blood pressure carrying with it a notable acceleration—in the absence of disturbing or complicating causes.

It may be remarked that similar changes are seen after the cardiac augmentor nerves have been divided; they are evidently essentially due to changes in the activity of the vagi.

It may also be noted that the *continuance* of an excessively low pressure will ultimately lead to a great slowing of the pulse rate—following on the primary acceleration—in virtue of the influence of such a condition of blood pressure on the cardiac rhythm already mentioned (A, *a*), so that an extreme and prolonged lowering of the blood pressure occurring when the heart is beating at an approximately normal rate causes first a remarkable acceleration of the pulse, which ultimately gives place to a slow rate of beat. The latter change may be counteracted by an abnormally high temperature if such is present.

III. On the Effects of Excitation of Afferent Nerves upon the Cardiac Rhythm.

The changes excited in the cardiac rhythm as a result of stimulation of afferent nerves in favourable circumstances may be either of the nature (A) of a slowing or (B) an acceleration of the heart beat; whether the former (A) or the latter (B) takes place varies according to the conditions present at the time—the particular nerve stimulated, the strength and suddenness of the stimulation, the exact degree of chloroform anæsthesia, and the state of the medullary centres in other respects.

Some Features in the Results of Stimulation of Afferent Nerves.

1. Speaking generally, excitation of visceral or splanchnic afferent nerves (*e.g.*, vagus, cervical sympathetic, abdominal splanchnic, &c.), is more readily effective in altering the cardiac rhythm under chloroform than excitation of somatic afferent nerves. The result may be acceleration or slowing, or an alternation of these, in the case of either class of nerves.

2. Moreover, there is a very important difference between the action of the splanchnic and that of the somatic afferent nerves upon the pulse rate. The acceleration resulting from a stimulation of somatic nerves is accompanied by signs of diffuse motor excitation as indicated by the occurrence of more or less general muscular contraction, whereas acceleration often results from stimulating splanchnic or visceral nerves when there are no concomitant movements and no sign of any association with general motor excitation at all. In curarised animals, such as have been used by the great majority of investigators, this difference would not of course be evident.

3. Again, strong sudden stimulation of an afferent nerve may cause marked slowing, while weaker and more gradual stimulation of the same nerve causes acceleration. *Cæteris paribus*, strong sudden stimulation is relatively more apt to cause slowing. (Of course this does not necessarily hold good with *natural* stimulation of various afferent nerves.)

4. Further stimulation of such nerves (*e.g.*, the brachial or intercostal) may cause notable slowing of the heart in suitable conditions of anæsthesia (in the period already referred to as the most favourable one); but they commonly cause acceleration as their *only* effect on the cardiac rhythm when the anæsthesia is rendered somewhat deeper; and at a still later phase the afferent excitation induces no change at all in the pulse rate. An excitation which causes slowing, followed by acceleration, of the heart, at a certain phase of anæsthesia, commonly fails to cause any slowing at all, but only acceleration—if any effect at all—when more chloroform has been given.

Mechanism through which Changes in the Cardiac Rhythm are induced by Afferent Impulses.

A. *Reflex Slowing.*—The essential mechanism of reflex slowing is clear enough, the change being due, as is commonly believed, to an increased activity of the vagus centre; it does not depend on alterations in the blood pressure, or asphyxial conditions, or on any influence of the augmentor nerves, for it may be readily excited in the usual way after these nerves have been cut.

B. *Reflex Acceleration.*—It is evident that this change might be due to an alteration in the regulating influence exercised by the central nervous system on the heart through the cardiac nerves (vagi and augmentors), or to changed conditions induced in the heart itself, or to a combination of such causes.

Influence of the Cardiac Augmentor Nerves and the Vagi.

I have come to the conclusion that the augmentor nerves do not play the essential part, *i.e.*, that the reflex acceleration is not essentially dependent upon excitation of the augmentor nerves.

The chief evidence on this point may be briefly stated as follows:—

1. *The latency and character of the acceleration which often results from excitation of afferent nerves may be entirely different from what has been shown by many observers to be characteristic of the action of the augmentor nerves.*—Stimulation of the latter is followed, as is well known, by a long latent period, and then a quickening or rhythm begins, and gradually increases to a maximum (5, 10, or 15 seconds after the beginning of the stimulation, usually); later, the acceleration declines and gradually disappears. But when an afferent nerve is excited, the resulting cardiac acceleration not unfrequently presents itself after an exceedingly short and hardly appreciable interval, occurring with remarkable suddenness, and at once, or almost at once, attaining a very high value, or, it may be, its maximum. Such cases, though by no means the most common ones as regards the results of afferent excitation, are sufficiently numerous and unmistakable to be highly significant in the present connexion, showing, as they do, features in the change of rhythm which differ most strikingly from those characteristic of the action of the augmentors, and which, on the other hand, correspond most closely with what occurs when the controlling influence of the vagi is diminished or removed.

In some cases the extensive acceleration which may follow stimulation of afferent nerves sometimes, after lasting for a variable period, suddenly gives place to a phase of slow heart beat, the reflex acceleration vanishing as abruptly as it had begun. A more or less rhythmical alternation of suddenly recurring phases of acceleration

and slowing may at times be seen, and strongly suggests the occurrence of corresponding variations in the activity of the vagus centre as their cause.

An assumed excitation of the augmentor nerves could not afford a probable explanation of these facts; and the evidence points very decidedly to changes in the activity of the vagus centre as the primary and paramount cause of both the slowing and the acceleration reflexly excited in the way referred to.

2. *The result of stimulation of afferent nerves after section of the vagi while the cardiac augmentor nerves remain intact.*—Section of the vagi in the cat leads to a great acceleration of the cardiac rhythm, the pulse rate rising to a maximal rate of 216–250; the maximum varying to some extent in different animals and in different circumstances.

In this condition, the augmentor nerves being uninjured, excitation of afferent nerves gives rise to no further acceleration. But this does not constitute any proof as to whether the augmentor nerves are reflexly excited by afferent stimulation or not. For the circumstances are not favourable for augmentor excitation being effective in causing any notable change in the cardiac rhythm. It is, indeed, quite clear, as shown by direct stimulation, that the augmentors *can* accelerate the heart after section of both vagi, *e.g.*, when the blood pressure is extremely low, and the cardiac rhythm slowed in consequence; their action is not confined to a counteracting of the controlling influence of the vagi upon the rhythmic mechanism. But when the vagi are cut, and the heart beats at the high maximal rate mentioned above, the blood pressure remaining high and the bodily temperature, the respiration, &c., being satisfactory, direct stimulation of the augmentor nerves is without any appreciable accelerating effect upon the pulse rate. In such circumstances then, when the heart is beating at its high (maximal) rate, the non-occurrence of acceleration in response to excitation of afferent nerves cannot be taken as evidence that the cardiac augmentor centre is not reflexly affected by afferent impulses.

It is necessary, therefore, to reduce the cardiac rhythm to a lower level, at which it might be expected (judging from the results of direct stimulation of these nerves) that a sudden reflex excitation of the augmentor nerves would be able to manifest itself by an appreciable effect on the pulse rate, if the changed pulse rate (acceleration) induced by afferent excitation is really due to an excitation of the augmentor nerves.

The heart may be kept beating at a moderate rate, the normal rate, or somewhat slower or faster than normal, with much regularity for periods of some length by slight continued stimulation of the vagus nerve in the neck, after both these nerves have been cut. When this

is done, an afferent nerve (which was found to give marked reflex acceleration as long as the vagi were intact) can now be stimulated as before, with the result of causing evident manifestations of general motor excitement, shown by the occurrence of marked convulsive movements; but in this case there is no cardiac acceleration. The moderate rhythm maintained by slight continued excitation of the vagus is not appreciably interfered with by stimulation of afferent nerves; and this negative result I have obtained in every experiment with complete constancy. It strongly opposes the idea that the sudden and extensive acceleration frequently seen on stimulating afferent nerves is due to a reflex action of the augmentor nerves; for, as soon as the vagi are cut, no reflex acceleration occurs, even when, as in these experiments, the heart was kept beating at a moderate rate, a condition favourable to the marked manifestation of the influence of augmentor excitation upon the cardiac rhythm.

3. *The results of excitation of afferent nerves, after section of the cardiac augmentor nerves, the integrity of the vagi not being interfered with.*—The augmentor nerves were cut by a mode of operative procedure already stated. That the vagi remained uninjured was shown by their being readily excited through a rise of blood pressure or by a suitable stimulation of certain afferent nerves, well marked slowing of the heart being evident in each case.

In this condition, the cardiac augmentors being now excluded, stimulation of afferent nerves, which caused acceleration prior to section of the augmentors, can still cause a very marked quickening of the pulse rate. In the case of the brachial or intercostal nerves, for example, stimulation (mechanical or electrical) leads, in favourable circumstances, to a very decided change in rhythm, provided as before that the stimulation is also effective in causing general motor excitation; an acceleration is speedily induced, frequently to the extent of 20 per cent., but sometimes much more.

In some cases a brief phase of cardiac slowing is also seen; and in other instances a more or less regular alternation of phases of slowing and acceleration presents itself. The same general relation already noted as obtaining between the strength and suddenness of the stimulation, the excitability of the medullary centres (depending on depth of anæsthesia), and the nature of the change in rhythm as regards the occurrence of slowing or acceleration, is again observable here; also the notable difference between the splanchnic and somatic nerves, as regards the constant association of general motor excitement with the reflex cardiac acceleration which occurs in the latter case, and the frequent absence of any such association in the former.

In short, the action of afferent excitation upon the cardiac rhythm, as far at least as its main features are concerned, is essentially similar whether the augmentor nerves are divided or intact.

It will be seen that the evidence yielded from these three different sources is in complete accord—the evidence derived from (1) a consideration of the nature of the cardiac acceleration which may occur, (2) the negative results obtained after section of the vagi, and (3) the (complementary) positive results seen in unmistakable form after exclusion of the augmentors while the vagi remain intact.

Possibility of Changes in the Peripheral Efficiency of the Vagi.

It remains to be seen how far a diminution of the controlling influence exercised by the medulla on the cardiac rhythm might be due to changes in the heart itself—changes leading to an impairment of the peripheral efficiency of the vagi, *e.g.*, the influence of the products of muscular contraction, or of altered conditions of intra-cardiac tension, especially in the right heart, depending on the occurrence of convulsive movements, &c.

As far as the splanchnic afferent nerves are concerned, these causes may be set aside, for, as has been already stated, reflex acceleration frequently occurs without any contraction of the skeletal muscles.

In the case of the stimulation of the somatic afferent nerves (where muscular contraction does occur) it is quite clear that the causes mentioned above are also unessential. Reflex acceleration sometimes occurs with an amount of muscular contraction far too slight to cause any such sudden alterations in either of the ways suggested; and, more, it may occur even after the skeletal muscles have been paralysed by curare. It has been already stated that there is no constant relation between the changes in blood pressure (frequently slight in amount) and the occurrences of reflex acceleration.

Further, I have examined the relation borne towards the peripheral efficiency of the vagi by (*a*) changes in arterial and intra-cardiac pressure and (*b*) well marked convulsive movements excited by stimulation of afferent nerves, after all the cardiac nerves have been cut, or the medulla destroyed or killed (cat or rabbit). The results have been as follows:—

a. Great and sudden changes in arterial pressure (*e.g.*, between 40 and 150 mm.) induced by compression of the descending thoracic or the upper part of the abdominal aorta, closure of the vena porta, &c., for short periods (*e.g.*, 30 secs.) though frequently accompanied by great changes in intra-cardiac tension had little or no appreciable effect upon the maintenance of the moderate or slow rate of beat maintained by slight continued excitation of the vagus in the neck.

b. The occurrence of very marked convulsive movements in response to stimulation of afferent nerves does not, even after several seconds, cause any perceptible change in the slowing influence of slight continued excitation of the vagus.

It is obvious that, whatever effects a *continuation* of altered intra-cardiac tension or muscular action may have upon the peripheral efficiency of the vagi, those causes are not in any way capable of accounting for such *sudden and extensive* reflex acceleration as is frequently seen when an afferent nerve is stimulated.

The primary and essential cause of the altered cardiac rhythm is clearly to be sought elsewhere, and it is obviously to be found in an altered activity of the central vagus mechanism. The acceleration depends on a diminution in activity of the vagus or cardio-inhibitory centre; just as the cardiac slowing is due to an increased activity of the same centre.*

Influence of Muscular Exertion upon the Cardiac Rhythm.

The striking association of cardiac acceleration with motor effort following excitation of afferent nerves distinctly suggests the existence of a somewhat close connexion between the motor mechanism and the cardiac regulating centres in the medulla. As has already been stated, the essential connexion is with the vagus centre; a diminished activity of that centre is associated with motor effort and leads to an accelerated heart beat.

And there is much to be said in favour of the hypothesis that a similar lessening of the controlling influence exercised by the vagus centre on the heart occurs during muscular exertion and constitutes at least *one* of the causes of the characteristic quickening of the pulse.†

It may be noted that in certain conditions of impaired health the heart becomes accelerated with extreme readiness from exertions, a very brief interval elapsing between the commencement of muscular actions and the change in cardiac rhythm. In some such instances it is difficult to find a feasible explanation either in an assumed influence of the products of contraction or in a supposed excitation of the augmentor nerves.

It is interesting to note that animals endowed with great staying powers (dog, horse, &c.) have, in many cases at least, a comparatively slow pulse rate in the quiescent condition; and that the heart is capable of an immense relative increase in the rate of its action as seen during muscular exertion or on section of the vagi. The con-

* Some recent observers (Roy and Adami, 'Phil. Trans.,' 1892) have assumed that the cardiac acceleration resulting from stimulation of afferent nerves may be taken as an indication of the action of the augmentor nerves on the heart. The untrustworthiness of this assumption—in the light of the results stated above—need hardly be commented on.

† It is hardly necessary to remark that *various* influences are probably concerned in determining the pulse rate during ordinary muscular exercise.

ditions present, in this connexion, in two such animals as the hare and the rabbit are very noteworthy. These animals, though very closely allied, from a zoological point of view, live under very different functional conditions in certain respects: the rabbit is able to run *short* distances with great rapidity, but not to traverse *long* distances without intermission—this being no doubt in relation to the fact of their having burrows to flee to; the hare, on the other hand, destitute of such means of protection, has to depend, in the open country, upon its endurance in swift locomotion. On examining the cardiac rhythm of this animal, I find it presents a remarkable contrast to that of the rabbit. In the latter animal, section of the vagi, as is well known, causes comparatively little acceleration. In the hare, on the other hand, in which the normal pulse-rate is much slower (*e.g.*, 64 per minute), the heart beats at an enormously increased rate (*e.g.*, 264 in the same animal) after the vagi have been divided.

In this animal, while the vagi are intact, the cardiac rhythm shows very sudden and extensive changes when the animal is disturbed, &c. These changes are probably due to alterations in the activity of the vagus centre.

Influence of Emotion upon the Cardiac Rhythm.

The characteristic acceleration of the heart induced by emotion in animals and in man is probably due, largely or mainly, to a diminished activity of the cardio-inhibitory centre. The acceleration is sometimes preceded by a phase of slowed action, due to excitation of the same centre, and the entire effects present a very striking resemblance to those induced by afferent impulses. This correspondence strongly suggests that the effects are, in the two cases, primarily dependent on similar causes—changes in the activity of the vagus centre—the primary slowing being due to a heightened activity of the centre and the subsequent acceleration to a reaction in the way of diminished activity—resembling what may be seen in certain other centres under the influence of emotional conditions. The suddenness and extent of the alterations in cardiac action sometimes induced by powerful emotion are easily applicable in connexion with such a view.

Conclusion.

From the evidence available on the subject, there is good reason to believe that, in addition to the well-known influences of blood pressure, asphyxial blood, &c., upon the vagus centre, the activity of that centre is affected either in way of increase or diminution by the play of afferent impulses from various parts, by impulses

(emotional, &c.,) from the higher parts of the central nervous system, and probably also, as far as a diminution of its activity is concerned, by the influence of some portion of the nervous mechanism concerned in the execution of muscular effort. And, as far as we know, it appears to be mainly upon the mediation of the vagus centre that the most important changes in the cardiac rhythm, in so far as determined by nervous influences, are primarily dependent.

V. "On the presence of Urea in the Blood of Birds, and its bearing upon the Formation of Uric Acid in the Animal Body." By Sir ALFRED GARROD, M.D., F.R.S. Received May 2, 1893.

Some experiments upon which I have recently been engaged have yielded results which appear to be inconsistent with any explanation yet advanced of the mode of formation of uric acid in the animal body, and to necessitate a new theory of its formation. These results I propose to discuss in the present paper, but before doing so it will be well to refer briefly to the different views upon this subject which have been from time to time advanced.

Until the year 1847 it was commonly supposed that uric acid was formed in the kidneys themselves, none having ever been detected in the blood, but in that year I succeeded in demonstrating the presence of uric acid in the blood of gouty subjects, which led to the conclusion that uric acid was formed in certain other organs and tissues of the body, and was merely eliminated by the kidneys.

It is now generally supposed that in mammals urea is produced as the ultimate product of the metabolism of nitrogenised tissues, the formation of a soluble urate being an intermediate stage of the metabolism; but that in birds the nitrogen is eliminated in the form of urate of ammonium without having undergone the further change into urea. Many efforts have been made to explain why these changes should be so different in animals of these two classes. A view once very popular and supported by great authority was that the difference could be accounted for by the amount of oxidation in the system; for example, it was assumed that, as respiration in the cold-blooded animals is slow and imperfect, the uric acid is not broken up, but is eliminated in the form of urate of ammonium; whereas in hot-blooded animals, such as the mammalia, the oxidation processes are more active and urea is produced. Those who held this opinion had in mind only the mammal and the reptile; altogether overlooking the fact that the bird, which throws out uric acid in the same way as the reptile, has even hotter blood and a more active respiration than the mammalia themselves. Hence this view had to be aban-